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(54) Title: STABILIZED COMPOSITION COMPRISING AN ANTIULCERATIVE BENZIMIDAZOLE

(57) Abstract

A stabilized composition comprising an antiulcerative benzimidazole compound, particularly a proton pump inhibitor, and a branched cyclodextrin-carboxylic acid.

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STABILIZED COMPOSITION COMPRISING AN ANTIULCERATIVE BENZIMIDAZOLE

FIELD OF THE INVENTION

The present invention relates to a stabilized composition containing an antiulcerative benzimidazole compound with enhanced water-solubility. Specifically, it relates to a stabilized composition containing an antiulcerative benzimidazole compound useful as medicaments or veterinary drugs, particularly antiulcerative agents, the stability of the composition and the water-solubility of the compound being enhanced by combining it with a branched cyclodextrin-carboxylic acid which is a cyclodextrin derivative.

BACKGROUND OF THE INVENTION

It is the most general and important problem in the field of pharmaceutics to enhance the water-solubility of water-insoluble or slightly water-soluble drugs and the stability of the composition containing the drugs. Cyclodextrins have been used as effective means to solve this problem. Cyclodextrins have been used for providing suitable volatility or improving taste or smell, or for emulsification,

powdering or stabilization, as well as for enhancing solubility of medicaments, etc. It is believed that these effects of cyclodextrins are produced by the formation of complexes containing active ingredients of pharmaceutical compositions, etc., in the cyclodextrins.

Various homologs of such cyclodextrins are known. Their water solubilities vary with their kinds. For example, α-, β- and γ-cyclodextrins consist of six, seven and eight glucose units, respectively, that are joined in such a way as to form a ring, and it is reported that the water-solubilities of α-, β- and γ-cyclodextrins are about 15%, about 2% and about 23%, respectively.

SUMMARY OF THE INVENTION

The present inventors have intensively studied how to enhance the water-solubility of antiulcerative benzimidazole compounds and the stability of the compositions containing the compounds. As a result, it has been found that use of a cyclodextrin having certain improved characteristics can achieve the above objects. Thus, the present invention has been completed.

The present invention provides a stabilized composition comprising an antiulcerative benzimidazole compound and a branched cyclodextrin-carboxylic acid or a salt thereof.

The present invention also provides a method of enhancing stability of a composition containing an antiulcerative benzimidazole compound, which comprises combining an antiulcerative benzimidazole compound with a branched cyclodextrin-carboxylic acid or a salt thereof.

The present invention also provides a method of enhancing solubility in water of an antiulcerative benzimidazole compound, which comprises combining the antiulcerative benzimidazole compound with a branched cyclodextrin-carboxylic acid or a salt thereof.

In the present invention, the antiulcerative benzimidazole compound is preferably a proton pump inhibitor, in particular lansoprazole or omeprazole. Preferably, the composition further comprises a pH adjusting agent, preferably meglumine. The composition is preferably an injectable composition, and is preferably miscible with a transfusion solution.

The composition of the present invention is particularly stable in a solid form, in particular a lyophilized form.

DETAILED DESCRIPTION OF THE INVENTION

The branched cyclodextrin-carboxylic acid to be used in the present invention is intended to include its free carboxylic acid, and a salt thereof with an alkali metal

(e.g., lithium, sodium, potassium, etc.), alkaline earth metal (e.g., calcium, magnesium, etc.), etc. These branched cyclodextrin-carboxylic acids can be used alone or in combination thereof, or as mixtures of their free carboxylic acids and salts thereof.

The branched cyclodextrin-carboxylic acid is a cyclodextrin having an organic group containing at least one carboxyl group at the 6-O-position of at least one glucose unit of the cyclodextrin ring.

The cyclodextrin ring in the branched cyclodextrin-carboxylic acid has, for example, 6, 7 or 8 glucose units. Preferably, the cyclodextrin ring has 7 glucose units. Examples of the cyclodextrin include α-cyclodextrin, β-cyclodextrin and γ-cyclodextrin.

It is preferred that the organic group containing at least one carboxyl group has 1 to 3 glucose units, and that at least one of the hydroxymethyl groups of the glucose units in the organic group is oxidized to a carboxyl group.

Examples of the branched cyclodextrin-carboxylic acid include 6-O-cyclomaltohexaosyl-(6→1)-α-D-glucosyl-(4→1)-O-α-D-glucuronic acid (cyclomaltohexaosyl-(6→1)-O-α-D-glucopyranosyl-(4→1)-O-α-D-glucopyranosiduronic acid) (hereinafter also abbreviated as α-CyD-G_2-COOH; the abbreviations of the following compounds are likewise shown in the parentheses), 6-O-cyclomaltoheptaosyl-(6→1)-α-D-

glucosyl-(4→1)-O-α-D-glucuronic acid (cyclomaltoheptaosyl-(6→1)-O-α-D-glucopyranosyl-(4→1)-O-α-D-glucopyranosiduronic acid)(β-CyD-G_2-COOH), 6-O-cyclomaltooctaosyl-(6→1)-α-D-glucosyl-(4→1)-O-α-D-glucuronic acid (cyclomaltooctaosyl-(6→1)-O-α-D-glucopyranosyl-(4→1)-O-α-D-glucopyranosiduronic acid)(γ-CyD-G_2-COOH), 6-O-cyclomaltohexaosyl-(6→1)-α-D-glucuronic acid (cyclomaltohexaosyl-(6→1)-O-α-D-glucopyranosiduronic acid)(α-CyD-G_1-COOH), 6-O-cyclomaltoheptaosyl-(6→1)-α-D-glucuronic acid (cyclomaltoheptaosyl-(6→1)-O-α-D-glucopyranosiduronic acid)(β-CyD-G_1-COOH), 6-O-cyclomaltooctaosyl-(6→1)-α-D-glucuronic acid (cyclomaltooctaosyl-(6→1)-O-α-D-glucopyranosiduronicacid)(γ-CyD-G_1-COOH), 2-O-(6-cyclomaltohexaosyl)-acetic acid (α-CyD-CH_2COOH), 2-O-(6-cyclomaltoheptaosyl)-acetic acid (β-CyD-CH_2COOH), 2-O-(6-cyclomaltooctaosyl)-acetic acid (γ-CyD-CH_2COOH), 3-O-(6-cyclomaltoheptaosyl)-propionic acid (β-CyD-CH_2CH_2COOH), 2-hydroxy-3-O-(6-cyclomaltoheptaosyl)-propionic acid (3-O-(6-cyclomaltoheptaosyl)-2-hydroxy-propionic acid)(β-CyD-$CH_2CH(OH)$-COOH), $7^A,7^C$-di-O-[α-D-glucuronyl-(1→4)-O-α-D-glucosyl]-(1→6)-maltoheptaose (β-CyD-$(G_2COOH)_2$), 6-O-cyclomaltoheptaosyl-O-α-D-maltosyl-(4→1)-O-α-D-glucuronic acid (cyclomaltoheptaosyl-(6→1)-O-α-D-glucopyranosyl-(4→1)-O-α-D-glucopyranosyl-(4→1)-O-α-D-glucopyranosiduronic acid)(β-CyD-G_3-COOH), and their salts described above (e.g., sodium salt

of β-CyD-G_2-COOH (sodium cyclomaltoheptaosyl-(6→1)-O-α-D-glucopyranosyl-(4→1)-O-α-D-glucopyranosiduronate (likewise abbreviated as β-CyD-G_2-COONa)).

Specifically, 6-O-cyclomaltohexaosyl-(6→1)-α-D-glucosyl-(4→1)-O-α-D-glucuronic acid (α-CyD-G_2-COOH), 6-O-cyclomaltoheptaosyl-(6→1)-α-D-glucosyl-(4→1)-O-α-D-glucuronic acid (β-CyD-G_2-COOH) and 6-O-cyclomaltooctaosyl-(6→1)-α-D-glucosyl-(4→1)-O-α-D-glucuronic acid (γ-CyD-G_2-COOH) are branched cyclodextrin-carboxylic acids containing α-cyclodextrin (containing 6 glucose units), β-cyclodextrin (containing 7 glucose units) and γ-cyclodextrin (containing 8 glucose units), respectively. In each of these branched cyclodextrin-carboxylic acid, maltose is attached to one of the glucose units of the cyclodextrin ring through an α-(1→6) linkage, and the hydroxymethyl group ($-CH_2OH$) at the 6-position of the terminal glucose unit of the maltose is oxidized to a carboxyl group to give glucuronic acid.

Each of 6-O-cyclomaltohexaosyl-(6→1)-α-D-glucuronic acid (α-CyD-G_1-COOH), 6-O-cyclomaltoheptaosyl-(6→1)-α-D-glucuronic acid (β-CyD-G_1-COOH) and 6-O-cyclomaltooctaosyl-(6→1)-α-D-glucuronic acid (γ-CyD-G_1-COOH) is a branched cyclodextrin-carboxylic acid in which glucose is attached to one of the glucose units of the cyclodextrin ring through an α-(1→6) linkage, and the hydroxymethyl group ($-CH_2OH$) at the

6-position of the branched glucose is oxidized to a carboxyl group to give glucuronic acid.

Further, 2-O-(6-cyclomaltohexaosyl)-acetic acid (α-CyD-CH_2COOH), 2-O-(6-cyclomaltoheptaosyl)-acetic acid (β-CyD-CH_2COOH) and 2-O-(6-cyclomaltooctaosyl)-acetic acid (γ-CyD-CH_2COOH) are preferable branched cyclodextrin-carboxylic acid wherein a carboxymethyl group is attached as a branch to one of the glucose units of the cyclodextrin ring.

These branched cyclodextrin-carboxylic acids or salts thereof are described in EP-A 0599646 (JP-A 7-076594) and in EP-A 0657176, and can be prepared, for example, by the methods described in the literatures.

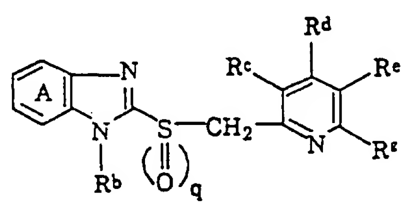
In the present invention, the water-solubility of an antiulcerative benzimidazole compound and the stability of the compositions containing the compound can be enhanced by formulating the compound together with a branched cyclodextrin-carboxylic acid.

The antiulcerative benzimidazole compound to be used is normally a proton pump inhibitor having a water-solubility of not more than 10 mg/ml.

The term proton pump inhibitor as used herein is defined as a drug that suppresses acid secretion by directly or indirectly inhibiting H/K-ATPase, which functions as a proton pump in gastric mucosal acid secreting cells (parietal cells). Representative examples of such drugs include

omeprazole, lansoprazole, pantoprazole, pariprazole sodium, leminoprazole, TY-11345, TU-199, FPL-65372, BY-686, Tannic acid, Ellagic acid, Ebselen, AHR-9294, Cassigarol-A, Bafilomycin, Y-25942, Xanthoangelol E, SK&F-96356, (-)-Epigallocatechin gallate, WY-27198, T-330 and KF-20054.

In detail, proton pump inhibitors include benzimidazole compounds, which possess proton pump inhibitory activities and are of low toxicity. Preferable benzimidazole compounds include 2-[(pyridyl)-methylsulfinyl or -methylthio]benzimidazole derivatives and salt thereof. A compound (or salt thereof) represented by formula (I) below is more preferred.



(I)

wherein ring A may optionally be substituted; R^b is a hydrogen atom, an alkyl group, an acyl group, a carboalkoxy group, a carbamoyl group, an alkylcarbamoyl group, a dialkylcarbamoyl group or an alkylsulfonyl group; R^c, R^e, and R^g are, the same or different, a hydrogen atom, an alkyl group, an alkoxy group or an alkoxyalkoxy group; R^d is a hydrogen atom, an alkyl group or a group represented by $-OR^f$ in which R^f represents a

hydrocarbon group which may optionally be substituted; q is 0 or 1.

Benzimidazole compounds above are described in USP 4,045,563, USP 4,255,431, USP 4,359,465, USP 4,472,409, USP 4,508,905, USP 5,039,806 (JP-A 59181277), USP 4,628,098, USP 4,738,975, USP 5,045,321, USP 4,786,505, USP 4,853,230, USP 5,045,552, EP-A-295603, USP 5,312,824, EP-A-166287, EP-A-519365, and other publications.

With respect to formula (I) above, the substituent that may optionally be present on ring A includes halogen atoms, alkyl groups which may be substituted for, cycloalkyl groups which may be substituted for, alkenyl groups which may be substituted for, alkoxy groups which may be substituted for, cyano groups, carboxy groups, carboalkoxy groups, carboalkoxyalkyl groups, carbamoyl groups, carbamoylalkyl groups, hydroxy groups, hydroxyalkyl groups, acyl groups, carbamoyloxy groups, nitro groups, acyloxy groups, aryl groups, aryloxy groups, alkylthio groups and alkylsulfinyl groups, and the like.

The above substituents are hereinafter described.

Halogen atoms include fluorine, chlorine, bromine and iodine. Fluorine and chlorine are preferred, with greater preference given to fluorine.

The alkyl group in the alkyl group which may be substituted is exemplified by straight-chain or branched alkyl

groups having 1 to 10 carbon atoms (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl). Straight-chain or branched alkyl groups having 1 to 6 carbon atoms are preferred, with greater preference given to straight-chain or branched alkyl groups having 1 to 3 carbon atoms. Substituents on the substituted alkyl group include halogens, nitro, cyano groups, hydroxy groups, carboxy groups, amidino groups, guanidino groups, carbamoyl groups, amino groups which may have 1 to 2 alkyl groups, acyl groups or other substituents, and the like.

The cycloalkyl group in the cycloalkyl group which may be substituted is exemplified by cycloalkyl groups having 3 to 7 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, etc. The cycloalkyl group may be substituted by, for example, halogens, nitro, cyano groups, hydroxy groups, carboxy groups, amidino groups, guanidino groups, carbamoyl groups, amino groups which may have 1 to 2 alkyl groups, acyl groups or other substituents, and the like.

The alkenyl group in the alkenyl group which may be substituted is exemplified by straight-chain or branched alkenyl groups having 2 to 16 carbon atoms. Such alkenyl groups include allyl, vinyl, crotyl, 2-penten-1-yl, 3-penten-1-yl, 2-hexen-1-yl, 3-hexen-1-yl, 2-methyl-2-propen-1-yl and

3-methyl-2-buten-1-yl. Straight-chain or branched alkenyl groups having 2 to 6 carbon atoms are preferred, with greater preference given to straight-chain or branched alkenyl groups having 2 to 4 carbon atoms. The alkenyl group may be substituted by, for example, halogens, nitro, cyano groups, amidino groups, guanidino groups amino groups which may have 1 to 2 alkyl groups, acyl groups or other substituents, and the like. The alkenyl group mentioned above includes isomers (E- and Z-configurations) with respect to double bond.

The alkoxy group in the alkoxy group which may be substituted is exemplified by alkoxy groups having 1 to 10 carbon atoms. Such alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, n-pentoxy, isopentoxy, neopentoxy, hexyloxy, heptyloxy, octyloxy, nonyloxy, cyclobutoxy, cyclopentoxy and cyclohexyloxy. Alkoxy groups having 1 to 6 carbon atoms are preferred, with greater preference given to alkoxy groups having 1 to 3 carbon atoms. The alkoxy group may be substituted by, for example, halogens, nitro, amidino groups, guanidino groups amino groups which may have 1 to 2 alkyl groups, acyl groups or other substituents, and the like

The halogen as a substituent on the above-described alkyl, cycloalkyl, alkenyl or alkoxy group is exemplified by chlorine, bromine, fluorine and iodine.

The alkyl group in the alkylamino group as a substituent on the above-described alkyl, cycloalkyl, alkenyl or alkoxy group is preferably exemplified by straight-chain or branched alkyl groups having 1 to 6 carbon atoms. Such alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, sec-butyl, n-pentyl, isopentyl, n-hexyl and isohexyl. Among other, straight-chain or branched alkyl groups having 1 to 4 carbon atoms are preferred.

The acyl group in the acylamino group as a substituent on the above-described alkyl, cycloalkyl, alkenyl or alkoxy group is exemplified by acyl groups derived from organic carboxylic acids, with preference given to alkanoyl groups having 1 to 6 carbon atoms. Such alkanoyl groups include formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl and hexanoyl, with greater preference given to alkanoyl groups having 1 to 4 carbon atoms.

The number of substituents on the above-described alkyl, cycloalkyl, alkenyl or alkoxy group is 1 to 6, preferably 1 to 3.

The substituted alkyl groups include trifluoromethyl, trifluoroethyl, difluoromethyl, trichloromethyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, methoxyethyl, ethoxyethy, 1-methoxyethyl, 2-methoxyethyl, 2,2-dimethoxyethyl, 2,2-diethoxyethyl and 2-diethylphosphorylethyl, among

others. Difluoromethyl, trifluoromethyl and hydroxymethyl are preferred, with greater preference given to trifluoromethyl.

The substituted cycloalkyl groups include 2-aminocyclopropan-1-yl, 4-hydroxycyclopentan-1-yl and 2,2-difluorocyclopentan-1-yl, among others.

The substituted alkenyl groups include 2,2-dichlorovinyl, 3-hydroxy-2-propen-1-yl and 2-methoxyvinyl, among others.

The substituted alkoxy groups include difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, 2-methoxyethoxy, 4-chlorobenzyloxy and 2-(3,4-dimethoxypehnyl)-ethoxy, among others. Difluoromethoxy is preferred.

The alkoxy group in the carboalkoxy group is exemplified by alkoxy groups having 1 to 7 carbon atoms (e.g., methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, n-pentoxy, isopentoxy, neopentoxy, hexyloxyl, heptyloxy).

The alkoxy group in the carboalkoxyalkyl group is exemplified by alkoxy groups having 1 to 4 carbon atoms (e.g., methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy). The alkyl group in the carboalkoxyalkyl group is exemplified by alkyl groups having 1 to 4 carbon atoms (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl). Such carboalkoxyalkyl groups include carbomethoxymethyl, 2-

carbomethoxyethyl, 2-carbomethoxypropyl, carboethoxymethyl, 2-carboethoxyethyl, 1-carbomethoxypropyl, carbopropoxymethyl and carbobutoxymethyl.

The alkyl group in the carbamoylalkyl group is exemplified by alkyl groups having 1 to 4 carbon atoms (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl).

The alkyl group in the hydroxyalkyl group is exemplified by alkyl groups having 1 to 7 carbon atoms (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, hexyl, heptyl).

The acyl group as such or the acyl group in the acyloxy group is exemplified by alkanoyl groups having 1 to 4 carbon atoms such as formyl, acetyl, propionyl, butyryl and isobutyryl.

The aryl group as such or the aryl group in the aryloxy group is exemplified by aryl groups having 6 to 12 carbon atoms (e.g., phenyl, naphthyl).

The alkyl in the alkylthio group or alkylsulfinyl group is exemplified by alkyl groups having 1 to 6 carbon atoms (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, hexyl).

The number of substituents on substituted ring A is preferably 1 to 4, more preferably 1 to 2. Such substituents on the benzene ring may be present at 4- and 5-positions, with preference given to 5-position.

Ring A is preferably a ring which may optionally be substituted by i) a halogen atom, ii) an alkyl group which may be substituted, iii) a cycloalkyl group which may be substituted, iv) an alkenyl group which may be substituted, or v) an alkoxy group which may be substituted.

The alkyl group for R^b is exemplified by alkyl groups having 1 to 5 carbon atoms (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl). The acyl group for R^b is exemplified by acyl groups having 1 to 4 carbon atoms, such as alkanoyl groups having 1 to 4 carbon atoms. The alkoxy in the carboalkoxy group is exemplified by alkoxy groups having 1 to 4 carbon atoms (e.g., formyl, acetyl, propionyl, butyryl, isobutyryl). The alkyl in the alkylcarbamoyl group and dialkylcarbamoyl group is exemplified by alkyl groups having 1 to 4 carbon atoms (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl). The alkyl in the alkylsulfonyl group is exemplified by the above-mentioned alkyl groups having 1 to 4 carbon atoms. R^b is preferably hydrogen.

The alkyl group for R^c, R^e or R^g is exemplified by straight-chain or branched alkyl groups having 1 to 10 carbon atoms (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl). Straight-chain or branched alkyl groups having 1 to 6 carbon atoms are preferred, with greater preference given to straight-chain or branched alkyl groups having 1 to 3 carbon atoms.

The alkoxy group for R^c, R^e or R^g is exemplified by alkoxy groups having 1 to 10 carbon atoms (e.g., methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, n-pentoxy, isopentoxy, neopentoxy, hexyloxy, heptyloxy, octyloxy, nonyloxy). Alkoxy groups having 1 to 6 carbon atoms are preferred, with greater preference given to alkoxy groups having 1 to 3 carbon atoms.

The alkoxy in the alkoxyalkoxy group for R^c, R^e or R^g is exemplified by alkoxy groups having 1 to 4 carbon atoms (e.g. methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy).

R^c is preferably a hydrogen atom, an alkyl group or an alkoxy group. R^e is preferably a hydrogen atom, an alkyl group or an alkoxy group. R^g is preferably a hydrogen atom.

The alkyl group for R^d is exemplified by alkyl groups having 1 to 4 carbon atoms (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl).

The hydrocarbon group in the hydrocarbon group which may optionally be substituted, for R^f, is exemplified by hydrocarbon groups having 1 to 13 carbon atoms, such as straight-chain or branched alkyl groups having 1 to 6 carbon atoms (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, pentyl, isopentyl, hexyl), alkenyl groups having 2 to 6 carbon atoms (e.g., vinyl, allyl, 2-butenyl, methylallyl, 3-butenyl, 2-pentenyl, 4-pentenyl, 5-hexenyl), alkynyl groups having 2 to 6 carbon atoms (e.g., ethynyl, propargyl, 2-butyn-1-yl, 3-butyn-2-yl, 1-pentyn-3-yl, 3-pentyn-1-yl, 4-pentyn-2-yl, 3-hexyn-1-yl), cycloalkyl groups having 3 to 6 carbon atoms (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl), cycloalkenyl groups having 3 to 6 carbon atoms (e.g., cyclobutenyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl), aralkyl groups having 7 to 13 carbon atoms (e.g., benzyl, 1-phenetyl, 2-phenetyl) and aryl groups having 6 to 10 carbon atoms (e.g., phenyl, naphthyl). Straight-chain or branched alkyl groups having 1 to 6 carbon atoms (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, pentyl, isopentyl, hexyl) are preferred, with greater preference given to straight-chain or branched alkyl groups having 1 to 4 carbon atoms.

The substituent group in the substituted hydrocarbon group is exemplified by C_{6-10} aryl groups (e.g., phenyl, naphthyl), amino, C_{1-6} alkylamino groups (e.g., methylamino,

ethylamino, isopropylamino), di-C_{1-6} alkylamino groups (e.g., dimethylamino, diethylamino), N-aralkyl-N-cycloalkylamino groups (e.g., N-benzyl-N-cyclohexylamino), N-aralkyl-N-alkylamino groups (e.g., N-(1-naphthylmethyl)-N-ethylamino), azide, nitro, halogens (e.g., fluorine, chlorine, bromine, iodine), hydroxyl, C_{1-4} alkoxy groups (e.g., methoxy, ethoxy, propoxy, butoxy), C_{6-10} aryloxy groups (e.g., phenoxy, naphthyloxy), C_{1-6} alkylthio groups (e.g., methylthio, ethylthio, propylthio), C_{6-10} arylthio groups (e.g., phenylthio, naphthylthio), cyano, carbamoyl groups, carboxyl groups, C_{1-4} alkoxycarbonyl groups (e.g., methoxycarbonyl, ethoxycarbonyl), C_{7-11} aryloxycarbonyl groups (e.g., phenoxycarbonyl, 1-naphthyloxycarbonyl, 2-naphthyloxy-carbonyl), carboxy-C_{1-4} alkoxy groups (e.g., carboxymethoxy, 2-carboxyethoxy), C_{1-6} alkanoyl groups (e.g., formyl, acetyl, propionyl, isopropionyl, butyryl, pentanoyl, haxanoyl), C_{7-11} alloyl groups (e.g., benzoyl, 1-naphthoyl, 2-naphthoyl), C_{6-10} arylsulfonyl groups (e.g., benzenesulfonyl, 1-naphthyl-sulfonyl, 2-naphthylsulfonyl), C_{1-6} alkylsulfinyl groups (e.g., methylsulfinyl, ethylsulfinyl), C_{6-10} arylsulfinyl groups (e.g., benzenesulfinyl, 1-naphthylsulfinyl, 2-naphthyl-sulfinyl), C_{1-6} alkylsulfonyl groups (e.g., methylsulfonyl, ethylsufonyl), 5- or 6-membered heterocyclic groups (e.g., 2-furyl, 2-thienyl, 4-thiazolyl, 4-imidazolyl, 4-pyridyl, 1,3,4-

thiadiazol-2-yl, 1-methyl-5-tetrazolyl) containing 1 to 4 heteroatoms (e.g., nitrogen, oxygen, sulfur), 5- or 6-membered heterocyclic carbonyl groups (e.g. 2-furoyl, 2-thienoyl, nicotinoyl, isonicotinoyl) containing 1 to 4 heteroatoms (e.g., nitrogen, oxygen, sulfur), 5- or 6-membered heterocyclic thio groups (e.g., 4-pyridylthio, 2-pyrimidylthio, 1,3,4-thiadiazol-2-ylthio, 1-methyl-5-tetrazolylthio) containing 1 to 4 heteroatoms (e.g., nitrogen, oxygen, sulfur). The heterocyclic thio group may condense with the benzene ring to form a bicyclic condensed thio group (e.g., 2-benzothiazolylthio, 8-quinolylthio). Halogens (e.g., fluorine, chlorine, bromine, iodine), hydroxyl and C_{1-4} alkoxy groups (e.g., methoxy, ethoxy, propoxy, butoxy) are preferred.

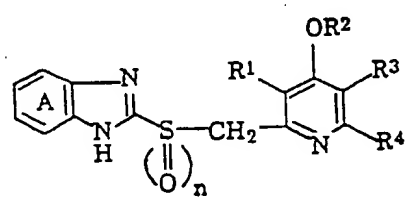
The number of substituents is normally 1 to 5, preferably 1 to 3.

R^d is preferably an alkoxy group which may be substituted, or an alkoxyalkoxy group which may be substituted. The alkoxy in the alkoxy group which may be substituted is exemplified by alkoxy groups having 1 to 8 carbon atoms (e.g., methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, n-pentoxy, isopentoxy, neopentoxy, hexyloxy, heptyloxy, octyloxy). The alkoxy in the alkoxyalkoxy group which may be substituted is exemplified by alkoxy groups having 1 to 4 carbon atoms (e.g., methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy,

sec-butoxy, tert-butoxy). R^d is more preferably an alkoxy group having 1 to 8, preferably 1 to 4 carbon atoms, which may be halogenated, or an alkoxyalkoxy group which may be halogenated. Preferred alkoxy groups which may be halogenated include 2,2,2-trifluoroethoxy, 2,2,3,3,3-pentafluoropropoxy, 1-(trifluoromethyl)-2,2,2-trifluoroethoxy, 2,2,3,3-tetrafluoropropoxy, 2,2,3,3,4,4,4-heptafluorobutoxy, 2,2,3,3,4,4,5,5,-octafluoropentoxy and methoxy. Preferred alkoxyalkoxy groups which may be halogenated include 3-methoxypropoxy.

q is preferably 0.

More specifically, the benzimidazole compound for the present invention is exemplified by a compound represented by formula (II):



(II)

wherein ring A may optionally be substituted; R^1, R^3 and R^4 are, the same or different, hydrogen, or an alkyl or alkoxy group; R^2 is a hydrocarbon group which may optionally be substituted; n is 0 or 1.

With respect to formula (II) above, ring A is exemplified by the same rings as those mentioned for ring A of formula (I) above.

The alkyl group for R^1, R^3 or R^4 is exemplified by straight-chain or branched alkyl groups having 1 to 10 carbon atoms. Such alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl and decyl. Straight-chain or branched alkyl groups having 1 to 6 carbon atoms are preferred, with greater preference given to straight-chain or branched alkyl groups having 1 to 3 carbon atoms.

The alkoxy group for R^1, R^3 or R^4 is exemplified by alkoxy groups having 1 to 10 carbon atoms. Such alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, n-pentoxy, isopentoxy, neopentoxy, hexyloxy, heptyloxy, octyloxy, nonyloxy, cyclobutoxy, cyclopentoxy and cyclohexyloxy. Alkoxy groups having 1 to 6 carbon atoms are preferred, with greater preference given to alkoxy groups having 1 to 3 carbon atoms.

The hydrocarbon group which may optionally be substituted, for R^2, is exemplified by the same hydrocarbon groups as those mentioned for R^f above.

R^1 is preferably C_{1-6} alkyl or C_{1-6} alkoxy, more preferably C_{1-3}.

R^3 is preferably hydrogen or C_{1-6} alkyl, more preferably hydrogen.

R^2 is preferably C_{1-4} alkoxy which may optionally be substituted by i) halogen, ii) hydroxyl or iii) C_{1-4} alkoxy, more preferably, C_{1-3} alkyl which may optionally be substituted by i) halogen or ii) C_{1-4} alkoxy.

R^4 is preferably hydrogen.

Examples of benzimidazole compounds for the present invention include 2-[2-[3-methyl-4-(2,2,3,3-tetrafluoro-propoxy)pyridyl]methylthio]benzimidazole, 2-[2-[3-methyl-4-(2,2,2-trifluoroethoxy)pyridyl]methylsulfinyl]benzimidazole (lansoprazole), 2-[(2-pyridyl)methylsulfinyl]benzimidazole (timoprazole), 2-[2-(3,5-dimethyl-4-methoxypyridyl)methyl-sulfinyl]-5-methoxy-1H-benzimidazole (omeprazole), sodium salt of 2-[2-[4-(3-methoxypropoxy)-3-methyl]pyridyl]methylsulfinyl-1H-benzimidazole and 2-[2-(3,4-dimethoxy)pyridyl]methyl-sulfinyl-5-difluoromethoxy-1H-benzimidazole (pantoprazole).

Among others, lansoprazole and omeprazole are preferably applied to the present invention.

A benzimidazole compound (or salt thereof) for the present invention is produced by, for example, the above-described known methods described in Japanese or European Patent Publications and U.S. Patents, or modifications thereof.

The salt of a benzimidazole compound is preferably used as a physiologically acceptable salt. Physiologically acceptable salts include salts with inorganic bases, salts with organic bases and salts with basic amino acids. Useful inorganic bases include alkali metals (e.g., sodium, potassium) and alkaline earth metals (e.g., calcium, magnesium). Useful organic bases include trimethylamine, triethylamine, pyridine, picoline, N,N-dibenzylethylene-diamine, ethanolamine, diethanolamine, trishydroxymethyl-aminomethane and dicyclohexylamine. Useful basic amino acids include arginine and lysine.

These salts are produced by known methods such as those described in EP-A-295603 and USP 4,738,974, or modifications thereof.

In the present invention, the mixing ratio of the branched cyclodextrin-carboxylic acid to the antiulcerative benzimidazole compounds is not limited and can be selected from wide ranges. However, considering the water-solubility of the compounds, the amount of the branched cyclodextrin-carboxylic acid to be used is 0.1 to 20 mol, preferably 0.1 to 10 mol, more preferably 0.2 to 5 mol, particularly preferably 2 to 5 mol, per mol of the antiulcerative benzimidazole compound.

The composition of the present invention can be prepared by mixing the branched cyclodextrin-carboxylic acid

with the antiulcerative benzimidazole compound according to known methods. Roughly speaking, the inclusion compound of the antiulcerative benzimidazole compound included in the branched cyclodextrin-carboxylic acid can be prepared, for example, by the following four methods:

(1) Co-precipitation method (Crassons, et al., 5th Int. Conf. Pharmaceutical Technology, Paris, May 30 to June 1, 1989),

(2) Lyophilizing or spray drying method (Kurozumi et al., Chem. Pharm. Bull., 23, 3062 (1975); Kata et al., Pharmazie 39, 856 (1984)),

(3) Phase - solubility curve crystallization method (Uekama et al., Int. J. Pharm. 10,1 (1982)),

(4) Milling method (J. Szejtli et al., "Cyclodextrins and their inclusion complexes", Akadeimial Kiado, Budapest (1982), p. 109-114; Kyowa Jap. Prov. Pat. Pubin. No. 106 698 (1982)).

Specifically, the inclusion compound can be prepared as follows:

(1) A compound to be included in the inclusion compound is added to an aqueous solution of the branched cyclodextrin-carboxylic acid (hereinafter sometimes referred to as the cyclodextrin). The mixture is stirred (shaken), if necessary, under warming. The remaining unreacted compound

to be included is removed by filtration, centrifugation, etc., to obtain an inclusion compound.

(2) The cyclodextrin is dissolved in water, and a compound to be included is added thereto. The two are mixed for 10 minutes to several hours, followed by lyophilization (M. Kurozumi et al., Chem. Pharm. Bull., 23, 142 (1975)) to give powder. This powder is dissolved in water, and the unreacted compound to be included is removed to obtain an aqueous solution of an inclusion compound.

(3) A compound to be included is dissolved in an appropriate water-soluble organic solvent in advance. This solution is contacted with cyclodextrin in an aqueous solution. Then the organic solvent and water are evaporated in vacuo or lyophilized (EP-A-519428, JP-A 5 (1992)-178765), and water is then added to the residue to dissolve it, and the unreacted compound to be included is removed to obtain an aqueous solution of an inclusion compound.

(4) When an acidic compound is included in the inclusion compound, it is dissolved in ammonia water and cyclodextrin is added thereto, and the mixture is lyophilized. During the lyophilization, excess ammonia is removed and an inclusion compound is obtained as an ammonium salt of the acidic compound.

(5) A compound to be included is dissolved in a lipophilic organic solvent (e.g., ethyl ether, etc.), and the

solution is mixed with a saturated aqueous solution of the cyclodextrin. The mixture is shaken vigorously for 10 minutes to several hours and then allowed to stand in a cold place overnight to precipitate an inclusion compound. The precipitate is separated by centrifugation or filtration. The resulting powder is dissolved in water to give an aqueous solution of an inclusion compound.

(6) A powdered compound to be included and powdered cyclodextrin are mixed, and a small amount of water is added thereto. The mixture is kneaded (Y. Nakai et al., Chem. Pharm. Bull., 26, 2419 (1978)) and then, if necessary, lyophilized.

(7) An aqueous solution of the cyclodextrin and an aqueous solution of a compound to be included are mixed to give an aqueous solution of an inclusion compound.

In particular, the above method (3) is useful for solubilization of antiulcerative benzimidazole compounds.

In many cases, the aqueous solution or powder thus obtained by the known methods giving inclusion compounds contains an inclusion compound or a complex formed by electrostatic or hydrophobic interactions or hydrogen bonds, etc. Therefore, the term "inclusion compound" used in the present invention means not only an inclusion compound or a complex per se but also a mixture of an inclusion compound, a complex, a free compound to be included and/or a free

cyclodextrin. That is, the powder and aqueous solution obtained may contain, other than an inclusion compound or a complex, a water-insoluble or slightly water-soluble compound that is not included or complexed, and/or free cyclodextrin. The inclusion compound per se and powder and an aqueous solution like this have extremely high water-solubilities and dissolve in water instantly.

The composition of the present invention may be the aqueous solution or powder per se thus obtained, or it may be a pharmaceutical composition in an appropriate dosage form, a veterinary composition, etc., prepared using known additives such as excipients, binders or lubricants.

For example, to improve properties of the powder obtained above (packing capacity into a storage bottle or a vial, specific volume, destaticizing, etc.), saccharides, antiseptics, stabilizers, antistatic agents, etc., can be added. For example, when injections are prepared, the powder obtained by this operation readily dissolves in an aqueous isotonic solution prepared using distilled water or sodium chloride and saccharides (e.g., glucose, mannitol, inositol, etc.). After dissolution, the resulting injectable preparation containing an active ingredient can be administered intravenously, intramuscularly, subcutaneously, into organs, or directly to foci such as tumor or excised parts of tumor, in a drug concentration effective in vivo

against the diseases to be treated. When oral preparations are prepared, tablets, capsules, granules, fine granules, enveloped preparations, drops, liquids, etc., can be prepared. On formulating these preparations, known excipients, lubricants, binders, dispersers, stabilizers, colorants and absorption-improving (promoting) agents, etc., can normally be used.

The above powder can also be formulated into preparations other than injectable or oral preparations according to conventional methods. Examples of such preparations are preparations administered to mucous membranes such as nose, the rectum. Each of the above preparations can be molded into various controlled-release preparations or preparations for targeting therapies, and the composition of the present invention can be used as a raw material of such preparations.

In the present invention, the composition is preferably an injectable composition, especially intravenously injectable solution. In terms of the stability of the composition, the composition preferably further contains a pH adjusting agent, such as meglumine, sodium hydroxide, potassium hydroxide, ammonia water, sodium bicarbonate, sodium carbonate, triethanolamine, monoethanolamine, diisopropanolamine, triisopropanolamine and L-arginine. The amount of the pH adjusting agent to be used is 0.01 to 10 mol,

preferably 0.1 to 5 mol, per mol of the antiulcerative benzimidazole compound. Preferably, the composition is miscible with a transfusion solution, and can be used as a mixture of the composition and a transfusion solution. Any commercially available or conventional transfusion solution can be used. Examples of the transfusion solution include glucose injection, xylitol injection, D-mannitol injection, fructose injection, isotonic sodium chloride solution, dextran 40 injection, dextran 70 injection, amino acid injection, Ringer's injection, lactated Ringer's injection. The ratio of the composition to the transfusion solution is 1/1 (v/v) to 1/500 (v/v), preferably 1/20 (v/v) to 1/100 (v/v).

As described above, the branched cyclodextrin-carboxylic acid used in the present invention enhances the water-solubility of antiulcerative benzimidazole compounds and has high safety to the living body. Therefore, the composition of the present invention is applicable to the prevention and treatment of animal ulcers, and is particularly effective in the prevention and treatment of digestive ulcers in mammals (e.g., humans, monkeys, cattle, dogs, swine, etc.). Examples of such digestive ulcers include gastric ulcer, duodenal ulcer, reflux esophagitis, anastomotic ulcer, acute and chronic gastritis. Specifically, for example, the composition comprising lansoprazole as the antiulcerative benzimidazole compound can be used in accordance with the

manner described in EP 0174726. The composition of the present invention can be administered in an appropriate dosage form such as injections, oralpreparations, syrups, preparations externally administered to skin, pernasal preparations, rectal suppositories or preparations applied to mucous membranes.

Although the dose of the composition of the present invention is chosen as appropriate, according to ulcer type, symptoms, age and the other factors, for example, in the case of the compositions of proton pump inhibitors, the compositions are administered at the dose of 0.01 mg/kg/day - 50 mg/kg/day, preferably 0.1 - 3 mg/kg/day, more preferably 0.1 - 1 mg/kg/day, as the dose of the proton pump inhibitors. Specifically, in the case of the composition of lansoprazole, the daily dose of lansoprazole is 0.01 - 30 mg/kg, more preferably 0.1 - 3 mg/kg.

The following examples further illustrate the present invention in detail, but are not to be construed to limit the scope thereof.

Example 1

Lansoprazole [(±)-2-[[[3-methyl-4-(2,2,2-trifluoro-ethoxy)-2-pyridyl]methyl]sulfinyl]benzimidazole] (19 mg) was dissolved in methanol (10 ml). Separately from this solution, sodium 6-O-cyclomatoheptaosyl-(6→1)-α-D-glucosyl-(4→1)-O-α-D-glucuronate (β-CyD-G_2-COONa)(384 mg) was dissolved in water

(10 ml). The aqueous solution was added to the methanol solution with stirring, and the mixture was stirred for 30 seconds. The solvent in the resulting solution was evaporated under reduced pressure. The residue was dissolved in water (2 ml), and the solution was filtered through a membrane filter (0.22 µm).

Separately, lansoprazole alone was added to water. The mixture was shaken at room temperature, and filtered through a membrane filter (0.22 µm).

The lansoprazole in the above homogeneous aqueous solution and filtrate was determined by high performance liquid chromatography (HPLC).

HPLC conditions:

Column	:	YMC AQ-312, 6 µm x 15 cm
Mobile phase	:	H_2O:CH_3CN:triethylamine = 60:40:1 (pH 7.0)
Flow rate	:	1 ml/min
Temperature	:	Room temperature
Detection	:	UV 285 nm

The results are as follows.

<u>Comparison of the water-solubility of the antiulcerative compound</u>

Lansoprazole combined with β-CyD-G_2-COONa	0.892 mg/ml
Lansoprazole alone	0.007 mg/ml

The results show that addition of β-CyD-G_2-COONa remarkably increased the water-solubility of the antiulcerative compound compared with the case in which the antiulcerative compound was used alone.

Example 2

Lansoprazole [(±)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]benzimidazole] (19 mg) was dissolved in methanol (5 ml). Separately from this solution, sodium 6-O-cyclomatoheptaosyl-(6→1)-α-D-glucosyl-(4→1)-O-α-D-glucuronate (β-CyD-G_2-COONa)(384 mg) was dissolved in water (5 ml). The aqueous solution was added to the methanol solution with stirring, and the mixture was stirred for 30 seconds. The solvent in the resulting solution was evaporated under reduced pressure. The residue was dissolved in water (10 ml), and the solution was filtered through a membrane filter (0.22 μm) and lyophilized to obtain powder. The powder (200 mg) was completely dissolved in water (200 ml).

The lyophilized composition comprising β-CyD-G_2-COONa and lansoprazole of the present invention was an inclusion compound which was stable at room temperature without decomposition of the lansoprazole.

Example 3

Lansoprazole [(±)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]benzimidazole] (300 mg) was dissolved in ethanol (50 ml). Separately from this solution,

sodium 6-O-cyclomatoheptaosyl-(6→1)-α-D-glucosyl-(4→1)-O-α-D-glucuronate (β-CyD-G_2-COONa)(6.05 g) and meglumine (1-deoxy-1-(methylamino)-D-glucitol)(600 mg) were dissolved in water (50 ml). The pH of the solution was adjusted to 11.5 with 1N NaOH. The ethanol solution was added to the aqueous solution with stirring, and the mixture was stirred for 60 seconds. The solvent in the resulting solution was evaporated under reduced pressure. The residue was dissolved in water (50 ml), and the solution was filtered through a membrane filter (0.22 µm) and lyophilized to obtain powder. The lansoprazole content in the resulting powder was 3.78% (w/w), and the water content in the powder was 10.9%.

Example 4

The lyophilized powder obtained in Example 3 was filled into vials (150 mg powder per vial) and dried over phosphorus pentaoxide, and each vial was sealed under an atmosphere of nitrogen gas. A preparative stability test was carried out at 40°C for 4 weeks. The water content was 0.5% after drying over phosphorus pentaoxide, and the amount of the residual lansoprazole was not less than 95% after 4 weeks.

Example 5

The lyophilized powder obtained in Example 3 was dissolved in water for injection (150 mg powder per ml of the water for injection). The solution was mixed with isotonic sodium chloride solution (Otsuka Seishoku Chu (Otsuka

Pharmaceutical Co., Ltd.)), glucose injection (Ohtsuka Toeki 5% (Otsuka Pharmaceutical Co., Ltd.)), Ringer's solution containing low molecular weight dextran and lactic acid (Low Molecular Weight Dextran L Injection (Otsuka Pharmaceutical Co., Ltd.)) and an electrolyte solution for transfusion (Solita T No. 3 (Shimizu Pharmaceutical Co., Ltd.)). The stability of lansoprazole after the addition of transfusion solution was tested. The composition ratio of the aqueous lyophilized powder solution to the transfusion solution was 1/99 (v/v). The amount of the residual lansoprazole was not less than 98% in the isotonic sodium chloride solution and glucose injection until 8 hours after the addition, not less than 97% in the Ringer's solution until 4 hours after the addition, and not less than 93% in the electrolyte solution for transfusion until 4 hours after the addition.

Example 6

The lyophilized powder obtained in Example 3 was dissolved in water for injection (150 mg powder per ml of the water for injection). The solution was added to each of Ringer's solution containing low molecular weight dextran and lactic acid (Low Molecular Weight Dextran L Injection (Otsuka Pharmaceutical Co., Ltd.)) and an electrolyte solution for transfusion (Solita T No. 3 (Shimizu Pharmaceutical Co., Ltd.)). The stability of lansoprazole after the addition of the transfusion solution was compared with that in a

formulation containing no cyclodextrin-carboxylic acid [the formulation being a solution of lyophilized powder of lansoprazole (30 mg) containing mannitol (60 mg) and meglumine (10 mg) in an aqueous 30% polyethylene glycol 400 solution (5 ml)]. The composition ratio of the aqueous lyophilized powder solution to the transfusion solution was 1/99 (v/v). The composition ratio of the formulation containing no cyclodextrin-carboxylic acid to the transfusion solution was 1/99 (v/v).

The amounts of the lansoprazole remaining 1 hour, 4 hours and 18 hours after the addition of the Ringer's solution containing low molecular weight dextran and lactic acid were 98.9%, 97.7% and 91.0%, respectively, in the case of the composition of Example 3, compared with 80.1%, 45.6% and 4.4%, respectively, in the case of the formulation containing no cyclodextrin-carboxylic acid.

The amounts of the lansoprazole remaining 1 hour, 4 hours and 18 hours after the addition of the electrolyte solution for transfusion were 98.2%, 93.3% and 62.3%, respectively, in the case of the composition of Example 3, compared with 60.1%, 12.8% and 0%, respectively, in the case of the formulation containing no cyclodextrin-carboxylic acid.

As described above, the composition of the present invention is very stable, and the antiulcerative benzimidazole compound combined with a branched cyclodextrin-carboxylic acid

according to the present invention has a much higher water-solubility compared with that of the antiulcerative benzimidazole compound alone. In addition, the branched cyclodextrin-carboxylic acid has less effect (e.g., destruction of erythrocytes) on the living body than β-cyclodextrin, and therefore is highly safe for blood. Moreover, β-CyD-G_2-COOH is hardly decomposed with acids or enzymes, and therefore the composition of the present invention is highly safe to mammals including humans.

CLAIMS

1. A stabilized composition comprising an antiulcerative benzimidazole compound and a branched cyclodextrin-carboxylic acid or a salt thereof.

2. A composition according to claim 1, wherein the antiulcerative benzimidazole compound is a proton pump inhibitor.

3. A composition according to claim 1, wherein the amount of the branched cyclodextrin-carboxylic acid is 0.1 to 20 mol per mol of the antiulcerative benzimidazole compound.

4. A composition according to claim 1, wherein the branched cyclodextrin-carboxylic acid is a cyclodextrin having an organic group containing at least one carboxyl group at the 6-O-position of at least one glucose unit of the cyclodextrin ring.

5. A composition according to claim 4, wherein the cyclodextrin ring has 7 glucose units.

6. A composition according to claim 4, wherein the organic group has 1 to 3 glucose units and at least one of the hydroxymethyl groups of the glucose unit(s) in the organic group is oxidized to a carboxyl group.

7. A composition according to claim 4, wherein the organic group is 2-carboxyethyl or 2-carboxy-2-hydroxyethyl.

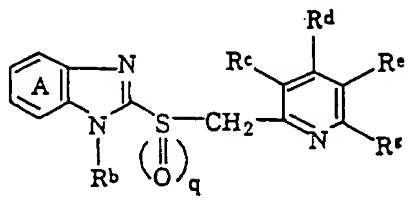
8. A composition according to claim 1, wherein the branched cyclodextrin-carboxylic acid is 6-O-cyclomaltohexaosyl-(6→1)-α-D-glucosyl-(4→1)-O-α-D-glucuronic acid, 6-O-cyclomaltoheptaosyl-(6→1)-α-D-glucosyl-(4→1)-O-α-D-glucuronic acid, 6-O-cyclomaltooctaosyl-(6→1)-α-D-glucosyl-(4→1)-O-α-D-glucuronic acid, 6-O-cyclomaltohexaosyl-(6→1)-α-D-glucuronic acid, 6-O-cyclomaltoheptaosyl-(6→1)-α-D-glucuronic acid, 6-O-cyclomaltooctaosyl-(6→1)-α-D-glucuronic acid, 2-O-(6-cyclomaltohexaosyl)-acetic acid, 2-O-(6-cyclomaltoheptaosyl)-acetic acid, 2-O-(6-cyclomaltooctaosyl)-acetic acid, 3-O-(6-cyclomaltoheptaosyl)-propionic acid, 2-hydroxy-3-O-(6-cyclomaltoheptaosyl)-propionic acid, $7^A,7^C$-di-O-[α-D-glucuronyl-(1→4)-O-α-D-glucosyl]-(1→6)-maltoheptaose, or 6-O-cyclomaltoheptaosyl-O-α-D-maltosyl-(4→1)-O-α-D-glucuronic acid.

9. A composition according to claim 1, wherein the branched cyclodextrin-carboxylic acid is 6-O-cyclomaltoheptaosyl-(6→1)-α-D-glucosyl-(4→1)-O-α-D-glucuronic acid.

10. A composition according to claim 1, which is a pharmaceutical composition.

11. A composition according to claim 1, which is an antiulcerative composition.

12. A composition according to claim 1, wherein the antiulcerative benzimidazole compound is represented by the formula (I):



(I)

wherein ring A may optionally be substituted; R^b is a hydrogen atom, an alkyl group, an acyl group, a carboalkoxy group, a carbamoyl group, an alkylcarbamoyl group, a dialkylcarbamoyl group or an alkylsulfonyl group; R^c, R^e, and R^g are, the same or different, a hydrogen atom, an alkyl group, an alkoxy group or an alkoxyalkoxy group; R^d is a hydrogen atom, an alkyl group or a group represented by $-OR^f$ in which R^f represents a hydrocarbon group which may optionally be substituted; q is 0 or 1.

13. A composition according to claim 1, wherein the antiulcerative benzimidazole compound is lansoprazole or omeprazole.

14. A composition according to claim 1, which further comprises a pH adjusting agent.

15. A composition according to claim 14, wherein the amount of the pH adjusting agent is 0.01 to 10 mol per mol of the antiulcerative benzimidazole compound.

16. A composition according to claim 1, wherein the pH adjusting agent is meglumine.

17. A composition according to claim 1, which is for injection.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 96/01427

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K47/48 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	EP,A,0 657 176 (TAKEDA CHEM. INDUST.) 14 June 1995 cited in the application	1
Y	see page 3, line 19 - line 55; claims 1,9 see page 6, line 14 - line 25 ---	1-23
Y	WO,A,86 00913 (BYK GULDEN LOMBERG CHEM FAB) 13 February 1986 see claim 1 ---	1-23
X	WO,A,95 07263 (SCHERING AG ;KUHNKE JOACHIM (DE); ECKLE EMIL (DE); THIERAUCH KARL) 16 March 1995 see claims ---	1,12
X,Y	DE,A,34 27 786 (BYK GULDEN LOMBERG CHEM FAB) 30 January 1986 see claims ---	1-23
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 July 1996	09.08.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Berte, M

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PCT/JP 96/01427

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,93 13138 (SUNKYONG IND CO LTD) 8 July 1993 see claims ---	1-23
X	DE,A,34 27 785 (BYK GULDEN LOMBERG CHEM FAB) 30 January 1986 see page 5, paragraph 2; claims -----	1,12

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/JP 96/01427

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		CN-A-	1111532	15-11-95
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